

REMARKS

Upon entry of the amendments herein, claims 1-11, 13-16, 19-37 and 45-75 are pending in the application. Claims 1, 4, 13-16, 32, 33, 34, 37, 45-52 and 58-60 have been amended; claims 12, 17 and 18 have been cancelled; and new claims 61-75 have been added. No new matter has been introduced by any of the amendments.

In the first place, Applicants and their agent acknowledge with gratitude the interview granted by the Examiner. The extraordinary amount of time taken by the Examiner to discuss and clarify the various outstanding issues is much appreciated. As discussed in detail below, the amendments herein to the claims are reflective of the discussions at the interview and the Examiner's input.

During the interview, all of the outstanding prior art rejections were discussed, and the Examiner discussed in greater detail the perceived overlap between the language of the instant claims and the disclosure of the prior art references that led her to level the rejections. The Examiner further made suggestions as to clarifications that could be made to the definitions of various components of the instant invention which would more clearly distinguish said invention over the cited prior art. The outstanding enablement issues were also discussed, and the Examiner provided further clarification and also suggestions for overcoming the

rejections. Particulars of the matters discussed during the interview are provided below in Applicants' responses to each of the rejections and by reference to the relevant claim amendments made herein.

In the interview discussion of the prior art rejection of claims 1, 26, 27 and 36 over Goldstein et al., it was pointed out to the Examiner that Goldstein does not teach, for example, the matrix-polymer component of the instant invention. The Examiner was further reminded of her own acknowledgement in Paper No. 6 that the Goldstein composition is lipid-ceramide based, and that this is nothing like the matrix polymer of the present invention. However, the Examiner countered with the assertion that "membranes are polymers of lipids," thus implying that the present scope of the matrix-polymer component as instantly claimed can be said to include such species as the sphingolipids of the Goldstein compositions.

In the first place, Applicants do not agree with the Examiner's assertion and implication. Applicants do not question that membranes can be composed of lipids. However, the concept of a membrane being a lipid polymer is at odds with the skilled artisan's understanding of what a polymer is, what a lipid is, and what is clearly intended by the term "polymer" by Applicants in disclosing and claiming the instant invention. One of the fundamental and universally recognized

characteristics of polymers is that the units of which they consist are covalently bound to each other. The lipid units that make up membranes are neither repetitive nor covalently bound. Furthermore, lipids themselves cannot be considered polymers.

This notwithstanding, Applicants have taken into account the Examiner's concern and have, in accordance with the Examiner's suggestion, amended claim 1 to more particularly define the matrix-polymer component; this component is now defined as comprising one or more homo- and/or copolymers. Support for this amendment can be found in the passage running from page 17, line 25 to page 18, line 2 of the specification.

The patentable distinction between the instant invention and Goldstein, already present in the claim language, has been further clarified by this amendment to claim 1, and there is no way that a valid case can be made that the latter disclosure inherently anticipates the former. The rejection should be withdrawn, and such withdrawal is respectfully requested.

In the discussion of the anticipation rejection of claims 1-3, 6, 7, 9 and 11-14 in view of U.S. Patent No. 4,610,868 to Fountain et al., it was pointed out to the Examiner that, for example, in the very first sentence of the FIELD OF THE INVENTION section (column 1, lines 46 and 47 of the

reference), it is stated that the "invention relates to novel lipid complexes and to their use as carriers in delivery systems." [Emphasis added.] In response, the Examiner again asserted that the invention as claimed does not exclude lipids as matrix-polymer material and further pointed out the disclosure in the instant specification that the stabilizing agent can be a lipid and that the matrix polymer can be used as a stabilizing agent. Again, however, as set forth above, the concepts of lipid and polymer are mutually exclusive, and one of skill in the art would not draw from the instant disclosure a connection between the matrix polymer of the instant invention and a lipid. In any event, the amendment made to claim 1 has more particularly described the instant invention, as the Examiner suggested, and has clarified the definition of the matrix-polymer component, thus making it unambiguously clear that there is no overlap between the instantly claimed invention and the "inherent" disclosure of Fountain alleged by the Examiner.

In the discussion of the anticipation rejection of claims 1, 3-6, 9, 12, 19, 20, 23-25, 32-38, 45-49 and 58 in view of WO 96/36317, the sentence starting the Summary of the Invention section (page 1, lines 26-29 of the reference) was pointed out to the Examiner. This sentence discloses that the "invention relates to a method for forming microparticles of a material from microdroplets of a solution, wherein the

solution comprises the material dissolved in a solvent." One would expect that the tertiary structure of a water-insoluble protein antigen would not be maintained when the method of the cited reference is used. The Examiner's view that the reference discloses a method for forming microparticles comprising vitamins is not questioned by Applicants. However, the Examiner's statement that "vitamins are known hydrophobic protein molecules" is completely without basis; it is common knowledge that vitamins are not proteins at all and are in a separate biochemical class (see, e.g., the enclosed excerpts from The Penguin Dictionary of Chemistry and the Dictionary of Biochemistry and Molecular Biology).

Therefore, Applicants maintain that the cited reference does not, as the Examiner asserts, inherently teach the instantly claimed invention. Nonetheless, claim 1 has further been amended along the lines suggested by the Examiner to more particularly recite the organic-solvent component of the instant invention by the addition of a further functional aspect to this component, an aspect which, as pointed out above, could not be a part of the system disclosed by the cited reference. Thereby, Applicants have addressed the concerns voiced by the Examiner, and the rejection is moot. Support for this amendment can be found on page 5, lines 27-29 of the specification. Furthermore, claim 75 has been added to recite specific examples of suitable organic-solvent

components. Support for this claim can be found on page 18, lines 20 and 21 of the specification.

In discussing the anticipation rejection of claims 1-4, 11-13, 19-23, 32-38, 45-50, 53, 55 and 58 in view of either of the "Genentech" references (WO 95/11009 and WO 95/11010), it was pointed out the Examiner that, for example, said references do not teach microencapsulation of water-insoluble protein antigens, nor is there any disclosure of stabilizing agents in the form of hydrophilic surfactants. It was further pointed out to the Examiner that the proteins disclosed in the "Genentech" examples are said to be delivered in Tris buffer. In other words, the proteins are delivered in aqueous solution, thus contradicting the notion that the cited references teach a system for delivering water-insoluble protein antigens.

All of this notwithstanding, the Examiner maintained the stance that the references inherently anticipate the invention as claimed at the time of the interview. Although Applicants do not agree with this assessment, in the interest of expediting prosecution of the application claim 1 has further been amended not only to recite that the solubilizing-agent component is a hydrophilic surfactant but to recite a specific range of critical micelle concentrations in which this component is present. The Examiner stated unequivocally during the interview that a recited combination of a water-

insoluble protein antigen and a hydrophilic surfactant would distinguish the instant invention from the cited "Genentech" references. Support for this amendment can be found on page 15, lines 12-18 of the specification. As a consequence of this amending of claim 1, claims 12, 17 and 18 are either redundant or outside the scope of claim 1 and have been canceled.

There are also two outstanding obviousness rejections in view of WO 96/36317 in combination with other references. The Examiner indicated that effective addressing of the anticipation issues would render moot the obviousness rejections as well. Accordingly, since the anticipation rejection in view of WO 96/36317 has been fully addressed by the amendments and arguments herein, the Bölin and Weers references are of no consequence in the present assessment of patentability. The invention as recited in the amended claims is without question distinct from the disclosure of the primary reference and, as the Examiner tacitly acknowledged during the interview, the additional cited teachings would not lead one to the instant invention.

With regard to the issues concerning the scope of enablement of the composition and method-of-treatment claims, the Examiner made it clear that the primary obstacle to allowance was the labeling of the compositions involved in these two sets of claims as vaccines. In accordance with the

Examiner's suggestion, the claims have been amended to eliminate recitation of vaccines. Claim 1 now recites a method for producing a system for delivery of water-insoluble antigens. Thus, the composition and method claims, ultimately dependent from claim 1, are also directed to antigen delivery. The composition claims have further been amended in this vein as required, and the method claims have been amended to recite induction of an immune response.

These amendments address the Examiner's expressed concerns about Applicants' showing of the effectiveness of the instantly claimed compositions as vaccines per se. In conjunction with the amending of the composition and method-of-treatment claims, Applicants have also added some new claims directed to more specific embodiments of the invention with respect to the protein antigens themselves. At the interview, the Examiner gave assurance that these claims would also be held allowable.

Finally, Applicants would like to emphasize a couple of points with respect to the novelty, unexpectedness and enablement of the instantly claimed invention. One of skill in the art would, if anything, have been led away from using a hydrophilic surfactant for the purpose of delivering water-insoluble protein antigens. The skilled artisan would have understood that the addition of such a component would destabilize the particles by interrupting the oil-water

interface, thus precluding incorporation of antigen for delivery. However, as shown particularly by the data presented in Figures 5 and 6 in the instant specification, the instant delivery system achieved significant incorporation of antigen and subsequent generation of significant antibody titer.

It should be noted that the instant antigen delivery system was compared in its immunogenic capacity with the "gold standard," i.e. the protein antigen combined with cholera toxin. Immunization with the instant delivery system produced a significant antibody titer when compared with said standard and demonstrated that, despite what would be expected based on the knowledge in the field, a significant amount of water-insoluble antigen was incorporated into the instant system and proved effective in generating an immune response.

This response also includes a Supplemental Information Disclosure Statement whereby Applicants make two new references of record.

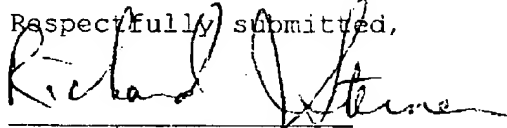
The instant claims have been amended in a number of ways to more particularly recite the subject matter regarded as the invention. This response fully addresses the issues raised by the Examiner. Reconsideration and allowance of the application with pending claims 1-11, 13-16, 19-37 and 45-75 are respectfully requested. Should any other matters require

attention prior to allowance, it is requested that the
Examiner contact the undersigned.

The Commissioner is hereby authorized to charge any fees
which may be due for any reason to Deposit Account No. 23-
1703.

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Respectfully submitted,



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Enclosures